REMARKS

Claims 10, 12-14, 16-20, 27-29, 31-37, 39-44 and 46-54 were pending. Applicants have amended claims 10, 31 and 37, to further clarify the invention. Amendments to claims 19, 27-29, 31 and 34-35 merely involve replacing the term "agglomerates" to singular form and correcting the tense agreement accordingly. Applicants have also added new claims 55-57. Support for the following amendments are found in the specification at least on page 5, lines 18-20 and line 28 through page 6, line 1; page 7, lines 24-27; and on page 13, lines 13-15. Applicants address each of the rejections in the Office Action, and respectfully request reconsideration in view of the amended claims.

Formal Matters

As a preliminary matter, Applicants respectfully reconsideration and withdrawal of the finality of the office action. According to MPEP § 706.07(b),

> "[I]t would not be proper to make final a first Office action in a continuing or substitute application where that application contains material which was presented in the earlier application after final rejection or closing of prosecution but was denied entry because (A) new issues were raised that required further reconsideration and/or search, or (B) the issue of new matter was raised."

In the Advisory Action mailed 04/06/2004, the proposed amendments were not entered because they allegedly raised new issues that would require further consideration and/or search. Thus, the finality of the first Office Action in the present continuation is improper, and Applicants request reconsideration and withdrawal of the finality of the office action.

Claim Rejections under 35 U.S.C. § 112, first and second ¶s

The Office rejected claims 10, 12-14, 16-20, 27-29, 31-32, 34-37, 39-44 and 46-54 under 35 U.S.C. § 112, second ¶, as allegedly being indefinite. In particular, the Office indicated that the term "randomly ordered" is indefinite. The amended claims do not include the term "randomly ordered," rendering this rejection moot.

The Office also rejected claims 31, 37, 39-44 and 46-52 under 35 U.S.C. § 112, first ¶, as allegedly failing to comply with the written description requirement because of the insertion of the term "Carr index." The amended claims do not include the term "Carr index," and merely indicate how compressibility is measured. Throughout the specification, compressibility is consistently measured as 100 times the ratio of the difference between tapped bulk density and loose bulk density to the tapped bulk density. For example, in Table 3, compressibility is measured as follows:

Loose bulk density	Tapped bulk density	(Tapped bulk density – Loose bulk density)	(Tapped bulk density – Loose bulk density) / Tapped bulk density	Compressibility (%)
0.39	0.44	0.05	0.05 / 0.44	11
0.42	0.47	0.05	0.05 / 0.47	11

The mere recitation of art-recognized definitions known at the time of filing is not considered new matter. See MPEP § 2163.07. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Office also made several rejections under 35 U.S.C. § 112, first ¶. On page 5, the Office indicated that claims 10-14, 16-20, 25 are rejected as allegedly being non-enabled, but does not provide reasons for the rejection. Applicants assume that the rejection under claim 25 is a typographical error, as this claim has previously been canceled. Applicants address the remaining enablement rejections in more detail below.

The Office indicated that claims 10, 12-14, 16-20 and 53-54 are enabled for potassium clavulanate but allegedly nonenabled for alkali metal clavulanates. (See, Office Action, page 5, second full ¶). As amended, the claims relate to an agglomerate of pharmaceutically acceptable alkali metal clavulanate crystals, which Applicants respectfully submit are enabled.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP § 2164.01. Furthermore, "[t]he test of enablement is not whether

any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (*Id.* citing *In re Angstadt*, 537 F.2d 498, 504)). Further, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." MPEP § 2164.06 (citations omitted). Also, compliance with the enablement requirement does not turn on whether an example is disclosed. MPEP § 2164.02.

As indicated from the MPEP, enablement does not depend on whether there is reason to expect the same crystallization behavior with any alkali metal clavulanates. Rather, enablement depends on whether any necessary experimentation is undue, or whether the specification provides a reasonable amount of guidance for the skilled person to practice the invention. Whether any necessary experimentation is "undue" depends on various factors, including but not limited to the breadth of the claims, the nature of the invention, the level of one of ordinary skill, the level of predictability in the art, and the quantity of experimentation needed to make or use the invention. MPEP § 2164.01(a).

In this case, pharmaceutically acceptable alkali metal clavulanate salts are known. (See e.g., U.S. patent 4,454,069 at col. 1:66 through col. 2:2). The nature of the invention requires a low level of skill (*e.g.*, contacting a solution or suspension of a pharmaceutically acceptable alkali metal clavulanate salt in a solvent or mixture of solvents, with one or more anti-solvents to cause precipitation of an agglomerate). Furthermore, the number of pharmaceutically acceptable alkali metal clavulanate salts is limited, and the quantity of experimentation is not undue. Thus, Applicants respectfully submit that the claims are enabled for alkali metal clavulanate salts, and request that this rejection be withdrawn.

Furthermore, the Office rejected claims 10, 12-14, 16-20, 27-29, 31-32, 34-37, 39-44 and 46-54 under 35 U.S.C. § 112, first ¶, as allegedly failing to comply with the written description requirement. Specifically, the Office indicated that the removal of the previous limitation of "high

water affinity" broadens the invention beyond what the specification teaches. Applicants must again respectfully disagree.

The amended claims specifically relate to agglomerates comprising an alkali metal clavulanate salt. The previous limitation of "high water affinity" was in reference to β-lactam agglomerate components. Because the amended claims specifically relate to agglomerates comprising clavulanate salt, the absence of the term "high water affinity" does not broaden the claims beyond what the specification teaches.

Claim Rejections Under 35 U.S.C. § 102

The Office rejected claims 37, 40-42, 44, and 46-52 under 35 U.S.C. § 102(b), as allegedly being anticipated by U.S. patents 4,454,069, 6,417,352, or 5,288,862. Applicants must respectfully disagree.

U.S. patent number 4,454,069 teaches potassium clavulanate as well-defined needles or waisted plates (See col. 5: 35-39), which have been excluded. The clavulanates in the '069 patent were prepared by a "normal" precipitation procedure in which the precipitating diluent is added to the solution of the material to be crystallized. For example, potassium ethyl hexanoate in isopropanol was added to a solution of t-butylamine salt of clavulanate acid acetone solvate dissolved in acetone. (See, '069 patent, Examples 3 and 4).

U.S. patent number 6,417,352 also teaches a process for preparing potassium clavulanates using a "normal" precipitation procedure. For example, a solution of potassium ethyl hexanoate in isopropanol is added to a solution clavulanic acid in isopropanol. (See e.g., '352 patent at col. 4:40-56). Although the '352 patent does not specify the form of potassium clavulanates prepared, conditions which would be expected to obtain needle forms were used.

In the processes of the '069 and '352 patents, the needles that are formed are relatively large crystals that may aggregate into loosely formed bundles. (See Exhibit 1, bottom photograph). In contrast, the crystals formed in the processes of the present application do not grow to relatively large needles, but form an agglomerate immediately after crystallization starts. As shown in the top

photograph in Exhibit 1, the crystals that agglomerate are small and no individual needles are formed. Because the '069 and '352 patents do not describe agglomerates comprising pharmaceutically acceptable alkali metal clavulanate crystals that are substantially free from non-agglomerate crystals in the needle form, the '069 and '352 patents do not anticipate claims 37, 40-42, 44 and 46-52. Accordingly, Applicants respectfully request that these rejections be withdrawn.

U.S. patent 5,288,861 teaches the preparation of potassium clavulanate rosettes using a reverse precipitation method where the clavulanate solution is added to the precipitating diluent in contrast to the "normal" precipitation procedure described above. (See '861 patent at col. 4:18-24). For example, a filtrate comprising potassium clavulanate in aqueous methanol is added to isopropanol/acetone. (See, '861 patent at Example 1). Because potassium clavulanates in rosette form have been excluded, the '861 patent does not anticipate 37, 40-42, 44 and 46-52. Thus, Applicants respectfully request that these rejections be withdrawn.

Furthermore, the Office also rejected claims 37, 39-44 and 46-52 under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 97/33564. Applicants must again respectfully disagree. As indicated in our previous response dated May 6, 2004, WO 97/33564 only describe agglomerates of penicillin V potassium, phenoxymethylpenicillin potassium, amoxicillin trihydrate, and cephalexin monohydrate. While these antibiotic agglomerates may be mixed with a second pharmaceutically active agent such as potassium clavulanate, the potassium clavulanate itself is not an agglomerate of crystals.

Specifically, WO 97/33564 teaches agglomerates of a β–lactam antibiotic other than potassium clavulanate which is mixed with potassium clavulanate in powder form. (See e.g., WO 97/33564 on page 9, lines 21-22; and page 11, lines 17-18). Because WO 97/33564 fails to teach agglomerate comprising potassium clavulanate crystals, claims 37, 39-44 and 46-52 are not anticipated. Thus, Applicants respectfully request that this rejection be withdrawn.

Further, the Office rejected claims 10, 12-14, 16-19, 27-29, 31-32, 37, 42-44 and 51-54 under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 98/21212. The Office also

indicated that "[t]he lifting of the requirement for being highly hygroscopic broadens the claims. (Office Action, page 9). Applicants must respectfully disagree.

As previously indicated, the amended claims specifically relate to agglomerates comprising a pharmaceutically acceptable alkali metal clavulanate salt. The previous limitation of "high water affinity" was in reference to β-lactam agglomerate components. Because the amended claims specifically relate to agglomerates comprising clavulanate salt, the absence of the term "high water affinity" does not broaden the claims beyond what the specification teaches. Furthermore, WO 98/21212 teaches formation of rosette or needle formed crystals (See WO 98/21212 at page 4:16-18 and Example 8), which have been excluded. Thus, Applicants respectfully submit that claims 10, 12-14, 16-19, 27-29, 31-32, 37, 42-44 and 51-54 are not anticipated under WO 98/21212, and request that this rejection be withdrawn.

New claims 55-57

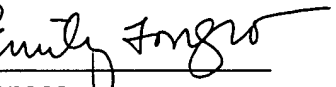
Applicants also submit that new claims 55-57 are free of prior art. None of the art the Examiner cited teaches a process comprising contacting potassium clavulanate in water or ethanol, and mixing the resulting solution with an anti-solvent to cause precipitation of a potassium clavulanate agglomerate that is substantially free from non-agglomerate crystals in the needle form and is other than potassium clavulanate rosette crystals. Thus, Applicants respectfully request allowance of new claims 55-57.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 246152015300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 24, 2004

Respectfully submitted,

By 

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